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L19: Entry 25 of 68

File: USPT

Jan 25, 2000

DOCUMENT-IDENTIFIER: US 6017734 A

TITLE: Unique nucleotide and amino acid sequence and uses thereof

Detailed Description Paragraph Right (331):

This example utilizes the ability to direct ODV to the target cell by incorporating receptors, fusion proteins etc. into the ODV envelope. Upon fusion with the host cell membrane the viral nucleocapsid is released into the host cell. When genes encoding therapeutic agents are genetically engineered into the viral genome under the control of promoters that are recognized by the host cell (i.e. baculovirus IE1 gene promoter), then this system can be utilized for gene delivery purposes. The obvious example uses gp120 and the AIDS virus. Engineering ODV to have a 23-CD4 receptor located on the viral envelope, enables the targeting of that virus directly to HIV infected cells. After membrane fusion with the HIV infected cell, a gene that is under the control of an appropriate promoter encoding an anti-HIV toxic protein could be delivered and expressed. The resultant protein production would mediate the killing of the HIV infected cell.

L7 ANSWER 5 OF 5 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.  
 AN 1991:182486 BIOSIS  
 DN BA91:97235  
 TI CHARACTERIZATION OF A CONSERVED T CELL EPITOPE IN HIV-1 GP41  
 RECOGNIZED BY VACCINE-INDUCED HUMAN CYTOLYTIC T CELLS.  
 AU HAMMOND S A; OBAH E; STANHOPE P; MONELL C R; STRAND M; ROBBINS F M; BIAS  
 W B; KARR R W; KOENIG S; SILICIANO R F  
 CS DEP. MED., JOHNS HOPKINS UNIV. SCH. MED., BALTIMORE, MD. 21205.  
 SO J IMMUNOL, (1991) 146 (5), 1470-1477.  
 CODEN: JOIMA3. ISSN: 0022-1767.  
 FS BA; OLD  
 LA English  
 AB A human CTL epitope located in a region of the HIV-1 envelope  
 protein gp41 that is highly conserved among various HIV-1  
 strains was identified. This epitope was recognized by CD4+ CTL  
 clones that were induced in seronegative humans by immunization with  
 recombinant gp160. **Fusion proteins** carrying portions  
 of the HIV-1 env gene and synthetic peptides were used to  
 localize this epitope to amino acids 584-595 of the HIV-1 BRU  
 env sequence. Only two positions within this epitope showed variation  
 among North American HIV-1 isolates, and the substitutions were  
 conservative in nature. The Lys to Arg substitution at position 593  
 abolished recognition, probably by interfering with the peptide-MHC  
 interactins. This epitope was recognized in association with at least one  
 subtype of the widely distributed human class II MHC specificity DPw4,  
 namely DPw4.2. The relatively high frequency of this allele (27.2% among  
 Caucasians) makes it likely that a larger fraction of the population  
 would generate a response directed at this epitope than would be the case for  
 epitopes recognized in the context of gene products of most other class  
 II and class I loci. Interestingly, the closely related DP .beta.-chain  
 allele types 4.1 and 2.1, which differ from 4.2 by 3 and 1 amino acids,  
 respectively, were unable to present this gp41 peptide to  
 DPw4.2-restricted clones. Comparison of the structure of this epitope  
 with that of other peptides recognized in the context of DPw4.2 led to the  
 identification of a consenses sequence for DPw4.2 binding peptides.  
 Because the gp41 CTL epitope 584-595 identified here is highly conserved  
 and is recognized in the cntext of a common DP allele, it may represent  
 an important target region for **vaccine** development. Our results  
 indicate that **vaccines** containing their epitope may induce in a  
 significant fraction of those imunized CTL active against at least half  
 of all HIV-1 strains.

L11 ANSWER 3 OF 3 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.  
 AN 2000:38872 BIOSIS  
 DN PREV200000038872  
 TI Determinants of CD4 independence for a human immunodeficiency virus type  
 1  
 variant map outside regions required for coreceptor specificity.  
 AU LaBranche, Celia C. (1); Hoffman, Trevor L.; Romano, Josephine; Haggarty,  
 Beth S.; Edwards, Terri G.; Matthews, Thomas J.; Doms, Robert W.; Hoxie,  
 James A.  
 CS (1) Duke University Medical Center, LaSalle St. Ext., Durham, NC, 27710  
 USA  
 SO Journal of Virology, (Dec., 1999) Vol. 73, No. 12, pp. 10310-10319.  
 ISSN: 0022-538X.  
 DT Article  
 LA English  
 SL English  
 AB Although infection by human immunodeficiency virus (HIV)  
 typically requires an interaction between the viral envelope glycoprotein  
 (Env), CD4, and a chemokine receptor, CD4-independent isolates of  
 HIV and simian immunodeficiency virus have been described. The  
 structural basis and underlying mechanisms for this phenotype are  
 unknown.  
 We have derived a variant of HIV-1/IIIB, termed IIIBx, that  
 acquired the ability to utilize CXCR4 without CD4. This virus infected  
 CD4-negative T and B cells and fused with murine 3T3 cells that expressed  
 human CXCR4 alone. A functional IIIBx env clone exhibited several  
 mutations compared to the CD4-dependent HXBc2 env, including the striking  
 loss of five glycosylation sites. By constructing env **chimeras**  
 with HXBc2, the determinants for CD4 independence were shown to map  
 outside the V1/V2 and V3 hypervariable loops, which determine chemokine  
 receptor specificity, and at least partly within an area on the gp120  
 core  
 that has been implicated in forming a conserved chemokine receptor  
 binding  
 site. We also identified a point mutation in the C4 domain that could  
 render the IIIBx env clone completely CD4 dependent. Mutations in the  
 transmembrane protein (TM) were also required for CD4 independence.  
 Remarkably, when the V3 loop of a **CCR5**-tropic Env was  
 substituted for the IIIBx Env, the resulting **chimera** was found  
 to utilize **CCR5** but remained CD4 independent. These findings  
 show that Env determinants for chemokine receptor specificity are  
 distinct  
 from those that mediate CD4-independent use of that receptor for cell  
 fusion and provide functional evidence for multiple steps in the  
 interaction of Env with chemokine receptors. Combined with our  
 observation  
 that the conserved chemokine receptor binding site on gp120 is more  
 exposed on the IIIBx gp120 (T. L. Hoffman, C. C. LaBranche, W. Zhang, G.  
 Canziani, J. Robinson, I. Chaiken, J. A. Hoxie, and R. W. Doms, Proc.  
 Natl. Acad. Sci. USA 96:6359-6364, 1999), the findings from this study  
 suggest novel approaches to derive and design Envs with exposed chemokine  
 receptor binding sites for **vaccine** purposes.

L6 ANSWER 6 OF 16 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.  
 AN 2000:38872 BIOSIS  
 DN PREV200000038872  
 TI Determinants of **CD4** independence for a human immunodeficiency virus type 1 variant map outside regions required for coreceptor specificity.  
 AU LaBranche, Celia C. (1); Hoffman, Trevor L.; Romano, Josephine; Haggarty, Beth S.; Edwards, Terri G.; Matthews, Thomas J.; Doms, Robert W.; Hoxie, James A.  
 CS (1) Duke University Medical Center, LaSalle St. Ext., Durham, NC, 27710 USA  
 SO Journal of Virology, (Dec., 1999) Vol. 73, No. 12, pp. 10310-10319. ISSN: 0022-538X.  
 DT Article  
 LA English  
 SL English  
 AB Although infection by human immunodeficiency virus (**HIV**) typically requires an interaction between the viral envelope glycoprotein (Env), **CD4**, and a chemokine receptor, **CD4**-independent isolates of **HIV** and simian immunodeficiency virus have been described. The structural basis and underlying mechanisms for this phenotype are unknown. We have derived a variant of **HIV**-1/IIIB, termed IIIBx, that acquired the ability to utilize CXCR4 without **CD4**. This virus infected **CD4**-negative T and B cells and fused with murine 3T3 cells that expressed human CXCR4 alone. A functional  
 IIIBx env clone exhibited several mutations compared to the **CD4**-dependent HXBc2 env, including the striking loss of five glycosylation sites. By constructing env **chimeras** with HXBc2, the determinants for **CD4** independence were shown to map outside the V1/V2 and V3 hypervariable loops, which determine chemokine receptor specificity, and at least partly within an area on the gp120 core that has been implicated in forming a conserved chemokine receptor binding site. We also identified  
 a point mutation in the C4 domain that could render the IIIBx env clone completely **CD4** dependent. Mutations in the transmembrane protein (TM) were also required for **CD4** independence. Remarkably, when the V3 loop of a CCR5-tropic Env was substituted for the IIIBx Env, the resulting **chimera** was found to utilize CCR5 but remained **CD4** independent. These findings show that Env determinants for chemokine receptor specificity are distinct from those that mediate **CD4**-independent use of that receptor for cell fusion and provide functional evidence for multiple steps in the interaction of Env with chemokine receptors. Combined with our observation that the conserved chemokine receptor binding site on gp120 is more exposed on the IIIBx gp120 (T. L. Hoffman, C. C. LaBranche, W. Zhang, G. Canziani, J. Robinson,  
 I. Chaiken, J. A. Hoxie, and R. W. Doms, Proc. Natl. Acad. Sci. USA 96:6359-6364, 1999), the findings from this study suggest novel approaches  
 to derive and design Envs with exposed chemokine receptor binding sites for **vaccine** purposes.

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L6 ANSWER 16 OF 16 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.  
 AN 1995:108491 BIOSIS  
 DN PREV199598122791  
 TI Induction of antibodies to the human immunodeficiency virus type 1 by immunization of baboons with immunoglobulin molecules carrying the principal neutralizing determinant of the envelope protein.  
 AU Zaghouani, Habib; Anderson, Stephanie A.; Sperber, Kirk E.; Daian, Christina; Kennedy, Ronald C.; Mayer, Lloyd; Bona, Constantin A. (1)  
 CS (1) Dep. Microbiol., Mount Sinai Sch. Medicine, One Gustave Levy Place, New York, NY 10029 USA  
 SO Proceedings of the National Academy of Sciences of the United States of America, (1995) Vol. 92, No. 2, pp. 631-635.  
 ISSN: 0027-8424.  
 DT Article  
 LA English  
 AB The hypervariable region 3 (V-3) within the disulfide-bridged loop of the envelope protein of the human immunodeficiency virus type 1 (**HIV** -1) contains an amino acid sequence that was defined as a principal neutralizing determinant (PND). A 19-amino acid residue consensus sequence (designated V-3C) predicted from the PND sequences of 245 isolates as well as a sequence from the PND of the WMJ2 **HIV**-1 isolate (designated V-3M) were expressed on the variable region of murine-human immunoglobulin (Ig) **chimeras** that were designated Ig-V-3C and Ig-V-3M, respectively. The **HIV**-1 sequences on the Ig **chimeras** preserved their antigenicity and interacted with antibodies specific for peptides encompassing the V-3C and V-3M sequences. In baboons, Ig-V-3C and Ig-V-3M induced antibodies that bound V-3C and V-3M peptides as well as the glycoprotein gp120 envelope protein of **HIV**-1 MN isolate. In addition, the baboons' antisera were able to prevent infection of **CD4** Supt1 susceptible T cells by **HIV**-1 MN. Finally, Ig-V-3M **chimeras** were able to stimulate in vitro production of antibodies specific for the **HIV**-1 envelopederived peptides by lymphocytes from **HIV**-1-infected human subjects.

AN 1995:172497 BIOSIS  
 DN PREV199598186797  
 TI Immunogenic targeting of recombinant peptide **vaccines** to human antigen-presenting cells by chimeric anti-HLA-DR and anti-surface immunoglobulin D antibody Fab fragments in vitro.  
 AU Baier, Gottfried (1); Baier-Bitterlich, Gabriele; Looney, David J.; Altman, Amnon  
 CS (1) Inst. Med. Biol. Human Genetics, Univ. Innsbruck, Schoepfstr. 41, A-6020 Innsbruck Austria  
 SO Journal of Virology, (1995) Vol. 69, No. 4, pp. 2357-2365. ISSN: 0022-538X.  
 DT Article  
 LA English  
 AB To increase the inherently weak immunogenicity of synthetic peptide **vaccines**, we used recombinant DNA techniques to generate **chimeras** between immunogenic determinants of human immunodeficiency virus type 1 (**HIV-1**) gp120 and antibody Fab fragments reactive with surface structures displayed specifically on human antigen-presenting cells (APCs), including surface immunoglobulin D (sIgD) and class II major histocompatibility complex (MHC) molecules. Hybridomas producing anti-human MHC class II (HIA-DR) or surface immunoglobulin D monoclonal antibodies (MAbs) that recognize nonpolymorphic determinants were used to clone chimeric Fab gene fragments by employing an established procedure to generate antigen-binding Fab libraries in phagemid vector pComb3. Molecular and immunochemical analysis indicated that the expected chimeric Fab fragments expressing the **HIV-1** epitopes were correctly cloned and expressed in *Escherichia coli* and retained the binding specificity of the native (hybridoma-derived) MAb. The chimeric Fab fragments targeted the linked **HIV-1**-derived antigenic determinants to the surface of human APCs in vitro, as evidenced by fluorescence-activated cell sorter analysis. Furthermore, such recombinant immunotargeted **HIV-1** peptide antigens demonstrated improved immunogenicity over equivalent nonimmunotargeted control antigens, as shown by their ability to stimulate interleukin-2 production by **CD4+** T-helper cells from human donors exposed to **HIV-1** antigens. These data suggest that immunotargeting of recombinant peptide antigens via the attached Fab fragments facilitates uptake by human APCs with subsequent access to the MHC class II processing pathway thereby validating the immunotargeting concept for such recombinant subunit **vaccin**

L2 ANSWER 30 OF 100 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.  
 AN 1999:397214 BIOSIS  
 DN PREV199900397214  
 TI Envelope-dependent restriction of human immunodeficiency virus type 1 spreading in **CD4+** T lymphocytes: R5 but not X4 viruses replicate in the absence of T-cell receptor restimulation.  
 AU Vicenzi, Elisa (1); Bordignon, Paola Panina; Biswas, Priscilla; Brambilla, Andrea; Bovolenta, Chiara; Cota, Manuela; Sinigaglia, Francesco; Poli, Guido  
 CS (1) P2-P3 Laboratories, DIBIT, Via Olgettina 58, 20132, Milan Italy  
 SO Journal of Virology, (Sept., 1999) Vol. 73, No. 9, pp. 7515-7523. ISSN: 0022-538X.  
 DT Article  
 LA English  
 SL English  
 AB The human immunodeficiency virus (**HIV**) replicates in activated **CD4+** T lymphocytes. However, only **CD4+** Th2 and Th0, but not Th1, **CD4+** T-cell clones have been reported to efficiently support **HIV**-1 replication. This dichotomous pattern was further investigated in the present study in Th1, Th2, or Th0 cell lines derived from umbilical human cord blood and in T-cell clones obtained from the peripheral blood mononuclear cells (PBMC) of healthy adults. Both primary and laboratory-adapted **HIV**-1 strains with CCR5 as the exclusive entry coreceptor (R5 viruses) efficiently replicated in Th1, Th2, and Th0 cells. In sharp contrast, CXCR4-dependent (X4) viruses poorly replicated in both polarized and unpolarized **CD4+** T cells, including adults' PBMC infected several days after mitogenic stimulation. Unlike the X4 **HIV**-1NL4-3, a chimera in which the env gene had been replaced with that of the R5 **HIV**-1NL(AD8), efficiently replicated in both Th1 and Th2 cells. This X4-dependent restriction of **HIV** replication was not explained by either the absence of functional CXCR4 on the cell surface or by the inefficient viral entry and reverse transcription. T-cell receptor stimulation by anti-CD3 monoclonal antibodies fully rescued X4 **HIV**-1 replication in both Th1 and Th2 cells, whereas it did not alter the extent and kinetics of R5 **HIV**-1 spreading. Thus, R5 **HIVs** show a replicative advantage in comparison to X4 viruses in their ability to efficiently propagate among suboptimally activated T lymphocytes, regardless of their polarized or unpolarized functional profiles. This observation may help to explain the absolute predominance of R5 **HIVs** over X4 viruses

L2 ANSWER 12 OF 100 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.  
AN 2001:363571 BIOSIS  
DN PREV200100363571  
TI Uses of **CD4**-gamma2 and **CD4**-IgG2 chimeras.  
AU Maddon, Paul J.; Beaudry, Gary A. (1)  
CS (1) Upper Montclair, NJ USA  
ASSIGNEE: Progenics Pharmaceuticals, Inc.  
PI US 6187748 February 13, 2001  
SO Official Gazette of the United States Patent and Trademark Office  
Patents,  
(Feb. 13, 2001) Vol. 1243, No. 2, pp. No Pagination. e-file.  
ISSN: 0098-1133.  
DT Patent  
LA English  
AB This invention provides the **CD4**-IgG2 chimeric heterotetramer,  
wherein the heavy chains of the chimeric heterotetramer is encoded by the  
expression vector designated **CD4**-IgG2HC-pRcCMV (ATCC No. 75193).  
This invention also provides the **CD4**-IgG2 chimeric  
heterotetramer, wherein the light chains of the chimeric heterotetramer  
is encoded by the expression vector designated **CD4**-kLC-pRcCMV (ATCC  
No. 75194). This invention also provides the **CD4**-IgG2 chimeric  
heterotetramer, wherein the heavy chains of the chimeric heterotetramer  
is encoded by the expression vector designated **CD4**-IgG2HC-pRcCMV  
(ATCC No. 75193) and the light chains of the chimeric heterotetramer is  
encoded by the expression vector designated **CD4**-kLC-pRcCMV (ATCC  
No. 75194). Finally, this invention provides a method of inhibiting  
**HIV** infection of a **CD4**+ cell, a method of preventing a  
subject from being infected with **HIV**, and a method of treating a  
subject infected with **HIV** so as to block the spread of



L2 ANSWER 8 OF 100 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.  
AN 2001:522048 BIOSIS  
DN PREV200100522048  
TI Enhanced HIV-1 Gag immunogenicity by a DNA vaccine  
chimera with molecular adjuvants of the lysosomal-associated  
membrane protein (LAMP) and dendritic cell multi-lectin receptor (DC-MLR)  
in an AAV-ITR plasmid vector.  
AU Lu, Y. (1); Marques, E., Jr. (1); Chikhlikar, P. R. (1); August, J. T.  
(1)  
CS (1) Johns Hopkins School of Medicine, Baltimore, MD, 21205 USA  
SO Journal of Human Virology, (May June, 2001) Vol. 4, No. 3, pp. 154.  
print.  
Meeting Info.: 2001 International Meeting of the Institute of Human  
Virology Baltimore, Maryland, USA September 09-13, 2001 Institute of  
Human Virology  
. ISSN: 1090-9508.  
DT Conference  
LA English  
S